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10/576,266	12/20/2006	Sabine Gack	085449-0188	3606

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
HADDAD, MAHER M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,266	GACK ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-64* is/are pending in the application.

4a) Of the above claim(s) *32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 29-64 are pending.

2. Applicant's election with traverse of Group I, claims 29-31, directed to a method for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, and gestational diabetes, comprising determining the expression level of a peptide or polypeptide ADAM- 12 and the species of preeclampsia and PIGF, filed on 12/05/08, is acknowledged.

Applicant's traversal is on the grounds that the search and examination of the different groups of claims is not unduly burdensome to the examiner. Applicant traverses the species election on the grounds that the search and examination of all of the species does not impose an undue burden upon the examiner. Moreover, the M.P.E.P. provides that a reasonable number of species can be searched in one application. Applicant presumes that the species election is made to assist the Examiner in searching the invention, and that the Examiner will follow the procedures delineated in MPEP 809.02(c). This is not found persuasive because Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have a single general inventive concept and so lack unity of invention as set forth in the previous Office Action. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 32-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 29-31 are under examination as they read on a method for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, and gestational diabetes, comprising determining the expression level of a peptide or polypeptide ADAM- 12 and the species of preeclampsia and PLGF.

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

6. Applicant's IDS, filed 12/20/06, is acknowledged.

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Page 41, line 10 contains embedded hyperlinks and/or other forms of browser-executable code which are impermissible and require deletion.

8. The description of the figures on page 38, lines 10-25 is objected to because there is no corresponding Figure 8 in the drawings. Correction is required.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 29-31 are incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. In the instant case, no contacting step, no sample, no detection, no correlation step. It unclear how to determine the diagnosis of preeclampsia. No proper controls are setup to compare the healthy vs. disease of preeclampsia. It is not clear whether an increase of Adam12 or decrease of Adam12 is indicative of preeclampsia.

B) The term "the expression level, ligand or nucleic acid" recited in claim 31 lacks sufficient antecedent basis in base claim 29, base claim 29 only recites "the expression level of a peptide or polypeptide with a sequence selected".

C) Claim 29 is indefinite because it fails to specify whether "the expression level of a peptide or polypeptide" determined in the mother, father or the fetus is correlated to preeclampsia.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 29-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the diagnosis of preeclampsia comprising (a) obtaining a serum sample from a pregnant women in the late 2nd and early 3rd trimester, (b) contacting samples from pregnant women with anti-ADAM 12-S (SEQ ID NO:4) antibodies and (c) compare the level of ADAM 12-S in said serum sample to a gestational age-matched serum obtained form healthy women, wherein an increase in ADAM 12-S level in the serum is indicative of preeclampsia, does not reasonably provide enablement for a method for the diagnosis of a disease selected from the group consisting of preeclampsia, eclampsia, pregnancy induced hypertension, HELLP syndrome, intrauterine growth retardation, superimposed gestosis, and gestational diabetes, comprising determining the expression level of a peptide or polypeptide with a sequence selected from the group consisting of:
a) an amino acid sequence as presented in SEQ ID NO: 2 or 4;
b) an amino acid sequence exhibiting a sequence identity with any of the amino acid sequences according to a) of at least 85% over 100 amino acid residues; and
c) a fragment of any of the sequences defined above which is at least 5 amino acids in length, in claim 29, wherein the sequence is that shown in SEQ ID NO: 8 in claim 30, wherein the expression level, ligand, or nucleic acid is used in conjunction with a means or a diagnostic agent in claim 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

The specification on page 2, lines 26-34 lists several genes which have been reported to be either upregulated or downregulated during preeclampsia. The specification discloses that PLGF has been reported to be downregulated in blood serum, but not in placental tissue. The specification on page 3, lines 1-3, discloses that none of the genes cited above have been put into practice as routine markers for preeclampsia or related syndromes. The specification on page 3, lines 5-6, discloses that a reliable diagnosis of preeclampsia or related syndromes is not possible at the moment. The specification on page 3, lines 16-20, discloses that the problem underlying the present invention resides in providing a marker more indicative of preeclampsia and/or related syndromes than other markers. In particular, the problem resides in providing a highly indicative marker that can also be measured in body fluids. The specification on page 5, lines 25-29, discloses that ADAM 12-S is expressed highly in placenta and can be detected in blood serum during pregnancy, while it is undetectable in non-pregnancy serum (Shi et al, JBC, 275:18574-18580, 2000, IDS reference, in particular). However, no connection of ADAM 12, particularly

ADAM 12-S, to preeclampsia or a related syndrome has been reported previously. The Exemplification is drawn to Western Blot analysis of patients sera (see Example 13). Fig. 3 depicts elevated ADAM-12S protein levels in sera from patients diagnosed with preeclampsia Immunoblot analysis of gestational age-matched sera obtained from healthy (ctrl.) and preeclamptic (preecl.) pregnant women using an ADAM-12S specific rabbit polyclonal antibody. Samples are arranged according to the gestational age (GA) when sera were collected, as indicated on the top (gestational week plus additional days of pregnancy). Fig. 3 the gestational week started on week 25 (late 2nd trimester) 28, 29 and 32 (3rd trimester).

However, the claimed invention is directed to diagnosis of preeclampsia and a related disease comprising determining the level of ADAM 12-L, ADAM 12-S or fragments thereof, an amino acid sequence exhibiting 85% sequence identity over 100 amino acid residues of ADAM 12 or a fragment thereof of which is at least 5 amino acids in length.

However, besides ADAM 12-S (secreted), the specification fails show that ADAM 12-L or any ADAM 12 fragment is present in the sera from either preeclampsia or control even though the specification uses polyclonal antibodies that would detect the ADAM 12-L or any ADAM 12 fragment. It is known in the art that ADAM 12-L is a membrane-bound protein, and the skilled in the art would not expect to see the membrane-bound ADAM 12-L in any body fluid including sera. The specification fails to show any correlation between the ADAM 12-L or ADAM 12 fragment and any disease including preeclampsia. Yet, Applicant is claiming a method for the diagnosis of preeclampsia using ADAM 12-L (SEQ ID NO: 2) or any ADAM 12 fragment. While the specification uses polyclonal antibodies to detect ADAM 12-S, Figure 3 show not other bands that would qualify as 85% identical to claimed ADAM 12 polypeptides. Yet, Applicant claims determining the expression level of a peptide or polypeptide with a sequence comprising 85% identity with ADAM 12 or fragments thereof.

With respect to the lack of resolution step in the claims, the specification on page 5, lines 25-29, admits that ADAM 12-S is expressed highly in placenta and can be detected in blood serum during pregnancy, while it is undetectable in non-pregnancy serum. However, since ADAM 12-S is detected in blood serum during pregnancy while it is undetectable in a non-pregnancy serum, it cannot be seen how determining the expression level of ADAM 12-S would be indicative of preeclampsia. Specially, any pregnant women would have ADAM 12-S in her blood serum. It is unclear how the claims distinguish between pregnancy and the disease of preeclampsia.

Moreover, the US 20080292619 A teaches that the concentration of ADAM 12-S (meltrin α) detected in the serum from pregnant women was higher than that of the normal donor, and the concentration increased with the number of months of pregnancy (see ¶248). Accordingly, in the absence of proper control for the ADAM 12-S, an increase of ADAM 12-S would only indicate late pregnancy and not a disease of preeclampsia. In addition, Laigaard et al (Prenat Diagn 2003, 23:1086-1091) found that in first -trimester Down syndrom pregnancies, the concentration of ADAM12 was decreased (see abstract). Thus, it is not clear to the skilled in the art how to determine whether the ADAM 12 is a marker for Down syndrom or preeclampsia in the early stages of pregnancy.

In addition, US 20060134654, teaches that the *lower level* of ADAM12 in preeclampsia makes ADAM12 a useful risk marker for preeclampsia in the *first trimester screening study* (see ¶389-391 and 466-470, Examples 4 and 13). In summer, the pattern of ADAM 12-S indicates that reduced levels in early pregnancy (20060134654) with increasing levels in the late 2nd (25 gestational weeks) and early 3rd trimester (28-32 gestational weeks) (Fig. 3 of instant specification). From the instant claims, it is not clear what expression level of ADAM 12-S would diagnose preeclampsia. Fig. 3 of the instant specification discloses elevated ADAM 12-S protein levels in the sera from patients diagnosed with preeclampsia starting at gestational weeks 25-32). However, the instant specification is silent with respect to the pattern of ADAM 12-S level in early stages of preeclampsia.

The specification, on page 4, line 35, discloses that SEQ ID NO: 8, claimed in claim 30, is protein sequence region specific for the human ADAM 12-S. However, neither the specification nor the art has identified the 34 amino acids of SEQ ID NO: 8 to correlate with preeclampsia or any related diseases. The specification fails to determine the level of any peptide or polypeptide with SEQ ID NO: 8. In addition claim 29 also recites determining the expression level of a peptide exhibiting a sequence identity of at least 85% over 100 amino acid residues and a fragment of any of the sequences which is at least 5 amino acids in length. Besides ADAM 12-S of SEQ ID NO: 4, Applicant's results fail to show the expression level of any other peptide or polypeptide as claimed in claim 29 can be linked to preeclampsia.

Finally, at issue the sample, besides the mother blood serum sample, the specification fails to show any correlation between the ADAM 12 protein level and its increase in preeclampsia in any other sample obtained from fetus or father or maternal sample form any fluid body or tissue.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. Claims 29-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "a peptide or polypeptide with a sequence selected from the group consisting of: a) an amino acid sequence as presented in SEQ ID NO: 2 or 4; b) an amino acid sequence exhibiting a sequence identity with any of the amino acid sequences according to a) of at least 85% over 100 amino acid residues; and c) a fragment of any of the sequences defined above which is at least 5 amino acids in length, wherein the sequence is that shown in SEQ ID NO: 8, wherein the expression level, ligand or nucleic acid" as part of the invention.

In the instant case, however, there is no described or art-recognized correlation or relationship between the structure of the invention, the ADAM 12-L or any ADAM 12 fragments including SEQ ID NO: 8 and it's preeclampsia marker function, the feature deemed essential to the instant invention. Therefore, one of skill in the art would not envisage, based on the instant disclosure, the claimed genus of peptide or polypeptide which sequence as presented in SEQ ID NO: 2, any amino acid exhibiting a sequence identity with SEQ ID NO: 2 or 4 of at least 85% over 100 amino acid residues or a fragment of any of the sequences defined above which is at least 5 amino acids in length, or SEQ ID NO: 8, or the level of ligand or nucleic acid, which retain the features essential to the instant invention.

Applicant has disclosed only increase in amino acid of SEQ ID NO: 4 level in the sera for patients diagnosed with preeclampsia; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 5, 2009

/Maher M. Haddad/
Maher M. Haddad, Ph.D.
Primary Examiner
Technology Center 1600